REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claim 9 has been amended to remove "halogen" from the definition of R^2, which should have been removed previously but was inadvertently overlooked.

Claim 18 has been amended to remove the parentheses throughout, as requested by the Examiner. The undersigned respectfully disagrees with the Examiner's assertion that "claim 18 recites many limitations within parenthesis which is unclear if said limitations are part of the claim." It is submitted that the parenthetical phrases were used effectively in this claim to distinguish sub-sets of definitions, *i.e.*, definitions of variables introduced by the preceding variable definition. Nevertheless, in applicants' continuing effort to advance this application to allowance, the Examiner's request has been complied with, and all parenthetical definitions have been removed and replaced by commas, with minor wording changes where appropriate for clarity. The undersigned has tried to strictly comply with the prescribed "Manner of Making Amendments" as set out in MPEP § 714, particularly the alternate instruction that when five or fewer consecutive characters are deleted, "extra portions of text may be included before and after text being deleted, all in strike-through, followed by including and underlining the extra text with the desired change." Although most of the amendments made to claim 18 involve simply the removal of a "(" and the replacement of a ")" with a comma, the need to incorporate "extra portions of text" in the strike-out and underlined insertions makes it appear that far more major changes have been made to this claim. In fact, the changes are minor and do not (and are not intended to) change the scope or meaning of this claim in any respect.

It is readily apparent that no new matter has been added by these amendments, and entry of the same is believed to be in order and is respectfully requested.

COMMENTS ON DETAILED ACTION

In summary of the Examiner's remaining and new grounds for rejection and Applicants response thereto:

- The section 103 obviousness rejection over the Myers '969 patent has been maintained for the reason that the Examiner continues to assert that the term "thiophenoxy" used in two Myers '969 compounds denotes a "thiophene" ring attached to the quinazoline via an oxygen linker. It will be shown below that whether one construes the term "thiophenoxy" by its old common meaning or tries to interpret this term in context of more modern nomenclature, under no circumstances would "thiophenoxy" be construed as having a 5-membered heterocyclic "thiophene" ring rather than a phenyl ring, and this is confirmed as well by the dictionary definition relied upon by the Examiner. Accordingly, Myers '969 does not give rise to *prima facie* obviousness.
- The Mohammadi *et al.* reference, newly applied to the obviousness rejection of pharmaceutical composition claim 16 and method claim 17, states nothing more than is already stated in the specification at page 1, lines 11-14. In any event, this reference does not somehow transform the clear teaching that the Myers '969 compounds are directed toward the inhibition of CSF-1 and CSF-1 signalling in bone remodeling and haematopoesis, into a teaching that the compounds would produce an antiangiogenic and/or vascular permeability reducing effect.
- The Examiner has also dismissed the Rule 1.132 Wedge Declaration as being "insufficient" to overcome the obviousness rejection based on Myers '969, on the assertion that the compounds addressed in the declaration "are not the compounds relied upon for the previous 103 rejection." However, as noted above, this obviousness rejection is based on a misconception of the structure of the two Myers '969 compounds applied to the rejection, which compounds, if correctly construed, are irrelevant to the present claims and most certainly less relevant than the Myers '969 compounds addressed in the Wedge Declaration. The law is clear that any comparison must be made against the closest compound actually

disclosed in the prior art, whether or not the Examiner may have applied a different compound from the reference to the rejection.

- Newly cited and applied Manning et al., WO 87/04321 (cited on the Examiner's Notice of References Cited) is not at all newly cited in this application since it was previously cited by Applicants on the July 29, 2003 form PTO-1449 (document NR) and initialed on October 16, 2003 as having been considered by the Examiner. In any event, the enormity of the generic breadth of this 789 page reference (R^1-X-R^2, each of R^1 and R^2 encompassing a myriad of diverse alternatives) provides no meaningful guidance toward the presently claimed compounds, and even the closest disclosed compounds are so structurally distinct as to not give rise to *prima facie* obviousness. Moreover, the field of this reference (reduction of transpirational water loss from plants and increase of crop yield) would not be considered sufficiently analogous art to be properly applied to any rejection in this pharmaceutical application.
- The new section 112 grounds for rejection have been addressed and overcome by the above amendments.

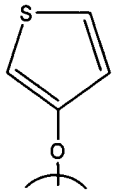
Claim Rejections - 35 USC § 103 - Myers '969

The rejection of claims 5-9, 13, 14, 18 and 19 as being unpatentable over Myers '969 under section 103(a) has been maintained in view of *Hawley's* Condensed Chemical Dictionary. In particular, the Examiner continues to assert that the term "thiophenoxy" in two compounds named in Myers '969 at column 9, lines 54 and 58, denotes a "thiophene-O" group, *i.e.*, a 5-membered heterocyclic thiophene ring linked via an oxygen to the 4-position of the quinazoline ring. The definition of the term "thiophenyl" in *Hawley's* is said to support this interpretation. Based on this interpretation, the Examiner asserts that the two compounds on lines 54 and 58 are analogous to those of present formula (II) in instant claims 5-9, 14 and 18, when Z_b is -O-; ring C is a 5-membered heterocyclic moiety (*e.g.*, thiophene); amd R^{2a} is alkoxy. The Examiner, acknowledges, nevertheless, that the disclosed compounds differ from

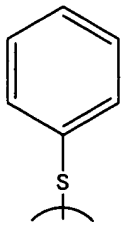
the claimed compounds by having a halogen or methoxy as a substituent corresponding to the instant variable R^2, which has been excluded from present independent claim 18.

This ground for rejection is respectfully traversed for the reason, *inter alia,* that under any technically plausible interpretation of the term "thiophenoxy," in context of both old and modern nomenclature, the ring in "thiophenoxy" is *not a thiophene ring*, but rather is a phenyl ring. This is clear from the *Hawley's* definition cited by the Examiner and from the IUPAC excerpt and other materials discussed below, and is consistent with the overall disclosure of Myers '969.

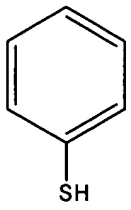
It is understood that the Examiner is asserting that the term "thiophenoxy" has the structure:



The Examiner offers nothing in support the above construction, but only attempts to refute Applicants' observation that "thiophenoxy" is the older commonly used term for the group "thiophenyl," wherein a **phenyl** ring (rather than a thiophene ring) is linked to the 4-position via sulfur:



The Examiner cites *Hawley's* definition of the term "thiophenol" as being the same as the term "phenyl mercaptan", which it lists as C_6H_5SH, *i.e.*:



and does not list a definition for "thiophenoxy" as thiophenyl as suggested by applicant.

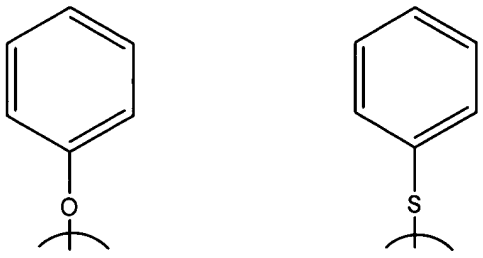
The point of this argument is not understood, in that it neither supports the Examiner's interpretation nor refutes Applicants' interpretation. *Hawley* and the Examiner are discussing "thiophen**ol**," a complete compound, whereas Applicants are discussing "thiophen**yl**" and "thiophenoxy," both being radicals or portions of a larger compound.

Note *Hawley's* definition of "thiophen**ol**" compared to "phen**ol**":

phen**ol** thiophen**ol**

where, in the "O" in the phenol is substituted by an analogously placed "S" in the thiophenol. In this older terminology, the thiophen**ol** is *not* a phen**ol** on which a thio "SH" group is additionally placed elsewhere on the ring, but rather the thiophenol substitutes the "O" of the phenol with an "S".

In an analogous manner, the radicals (molecule portions) denoted by the terms "phenoxy" and "thiophenoxy" have the following structures:



phenoxy thiophenoxy

where the "O" in the phenoxy group is substituted by an analogously placed "S" in the thiophenoxy group, consistent with Applicants' interpretation, and not at all supportive of the Examiner's assertion that the phenyl ring in phenoxy and thiophenoxy has somehow been transformed to a "thiophene" ring.

Support for the above analysis and conclusions, and refutation of the Examiner's unsupported assertion that a "thiophene" ring is somehow involved, is found, *inter alia*, in

the "Thiols and Related Compounds" Section C-5.1 of the IUPAC "Nomenclature of Organic Chemistry," 1995 printing. A copy of the title page and Section C-5.1 (pages 211-217) is attached.

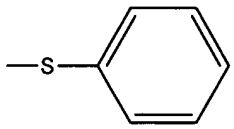
Attention is first drawn to page 212, Rule 511.2, which states, "The use of 'thio-' prefixed to the trivial name of a phenol, indicating replacement of the hydroxylic oxygen by sulfur, may be continued in simple instances, but the nomenclature of Rule C-511.1 is preferred." (Emphasis added). Rule C-511.1 provides the more modern nomenclature, stating in part, "When --SH is not the principal group, the prefix 'mercapto-' is placed before the name of the parent compound to denote an unsubstituted --SH group." Note also footnote * stating that "The class name 'mercaptan' is abandoned. The root is retained only in the prefix 'mercapto-' for an unsubstituted --SH group."

The text of IUPAC Rule C-511.1 also states, "Note: 'Thiol' is not to be confused with 'thiole' which denotes a five-membered ring embodying one sulfur atom." (Empasis added). It appears that this may be what the Examiner has done.

Other uses in the art consistent with Applicants' interpretation of the term "thiophenoxy" include:

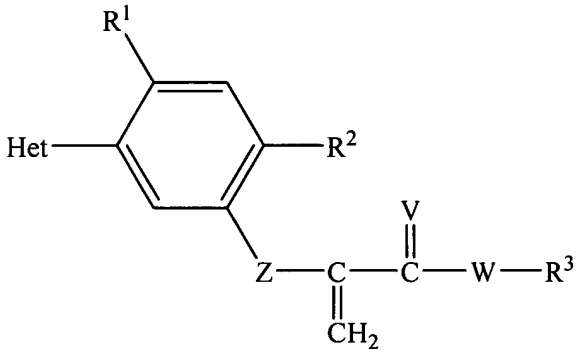
- US Patent 5,055,569, issued October 8, 1991, stating at column 7, lines 14-20:

  For the purpose herein the term "thiophenoxy" is used to mean the group having the structure:



- US Patent 6,528,455, issued March 4, 2003 based on an International Application filed December 15, 2000, published January 5, 2002, claiming priority from December 16, 1999, clearly demonstrates use of nomenclature in precisely the period in which the present invention was made. This patent is entitled, "PHENOXY- AND THIOPHENOXY ARCRYLIC ACID COMPOUNDS AS HERBICIDES." At column 1, lines 6-22, it is stated:

The present invention relates to 2-phenoxy- and 2-thiophenoxyacrylic acid compounds of the formula I

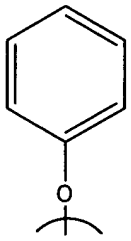


(I)

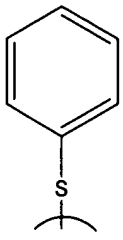
in which

Z, V and W independently of one another are oxygen or sulfur, . . .

In other words, when Z is oxygen, the structure represents a 2-phenoxyacrilic acid compound, and when Z is sulfur (the only alternative), the structure represents a 2-thiophenoxyacrylic acid compound. It is thus absolutely clear from this reference that common usage at the time of the present invention denoted the radical:

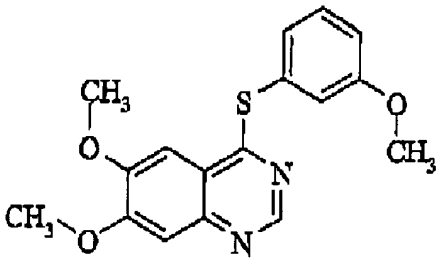


a phenoxy group (*i.e.*, Z is oxygen) and, consistently therewith, the radical:

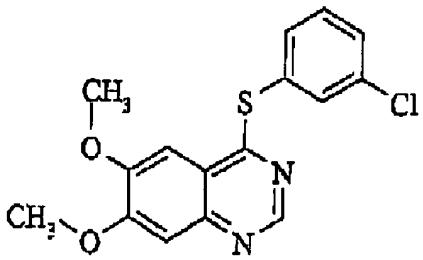


a thiophenoxy group (*i.e.*, Z is sulfur).

It is therefore respectfully submitted that it is clear from the above that the compounds at of Myers '969 at column 9, lines 54 and 58, have the structures:



4-(3-methoxythiophenoxy)-6,7-dimethoxyquinazoline



4-(3-chlorothiophenoxy)-6,7-dimethoxvquinazoline

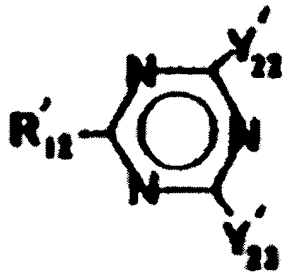
respectively, and very clearly do not have a thiophene ring anywhere in the 4-position substituent on the quinazoline ring. Accordingly, it is respectfully requested that the rejection of claims 5-9, 13, 14, 18 and 19 as being unpatentable over Myers '969 in view of *Hawley's* Condensed Chemical Dictionary be withdrawn.

Moreover, since the rejection of claims 16 and 17 over Myers '969 in view of Mohammadi is premised on the same misconception as to the structure of these two Myers '969 compounds, this ground for rejection should be withdrawn as well. While Applicants disagree with the Examiner's assertion that Mohammadi would somehow expand the very clear use taught by Myers '969 to suggest Applicants' quite different method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, this issue is now moot and need not be addressed at this time. It is well established that a composition containing, or a method using, a novel and unobvious compound would also be novel and unobvious be reason of the patentability of the compound claims.

Claim Rejections - 35 USC § 103 - Manning WO '321

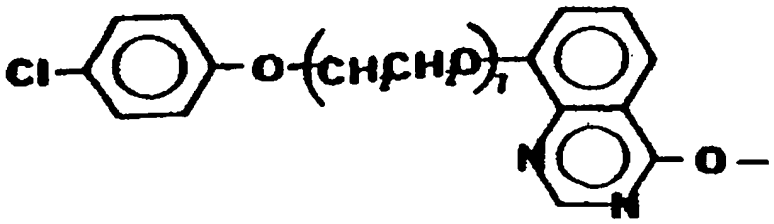
Claims 5-9 and 18 are newly rejected as being unpatentable over Manning *et al.*, WO 87/04321 under section 103(a). The Examiner characterizes the Manning reference as being "newly found" (Action at page 2) and lists it on the Notice of References Cited attached to the Action. Although it is believed that this reference would be considered "non-analogous art" under US practice,[1] the Examiner's attention is drawn to the fact that Applicants had previously formally cited this same Manning reference in the Information Disclosure Statement filed July 29, 2003 as document NR on the accompanying form PTO-1449, and the Examiner acknowledged consideration of this document on the initialed copy of that form PTO-1449 returned with the Action of October 22, 2003.

The Examiner specifically cites one compound from Table 14 (at page 117 of the Manning specification) as being "a triazolyl compound substituted with a quinazolin-oxy." The imaged structures in this reference are very difficult to read, so they will be greatly expanded below. It is believed that the compound referred to by the Examiner has the triazol ring common to the compounds of Table 14:



wherein the group R'_{12} is shown with the following structure:

[1] Manning discloses as the only use for its compounds the reduction of transpirational water loss from plants and increase of crop yield, which is an entirely different field from the specific medicinal use of the presently claimed compounds, and clearly non-analogous. However, as detailed below, the present compounds are clearly quite structurally distinct from the presently claimed compounds, and this will be the focus of the remaining remarks.



and Y'_{22} is said to be Cl and Y'_{23} is said to be CH_3SO_2. The Examiner asserts that "said compound is analogous to the compound of the instant formula II with the following substituent:

Z_b is -O-;

Ring C is a 6-membered heteroaryl group (e.g. triazinyl)."

The Examiner acknowledges that this compound differs from the instant formula II:

> ... by having a substituent at the 8th position, not the 7th position on the quinazoline ring. Also, the disclosed compound idffers from the instant formula II by having a substituent of CH_3SO_2 on the triazinyl ring which is not a moiety represented by the instant variable R^1. However, on columns [pages?] 5-13, the reference discloses a generic formula 1 of R_1-X-R_2, in which both R_1 and R_2 can be a heteroaryl group substituted with a substituent Z that can be **anywhere on the ring** (e.g., see pages 25 and 30). The substituent Z can be any moiety listed on page 13 which includes *hydroxy, cyano, nitro, trifluoromethyl,* etc. Thus, the generic disclosure provides equivalent teaching for many moieties as a substituent on ring R_1 or R_2, as well as for all the positions on both rings."

(Action at page 5, bold and italic emphasis in original; underlined emphasis added).

With all due respect, it is believed that the Examiner's characterization of this compound and the acknowledged differences from the presently-claimed compounds *itself* clearly demonstrates that there is no guidance in this reference that would lead the skilled person to make any compound as presently claimed. Moreover, the Examiner's reference to generic formula 1 on pages 5-13, and the substituents Z on page 13, does not even begin to indicate the breadth of these moieties, in that the permissible structures for R_1 and R_2 and the

myriad of permissible substituents extend from there all the way to page 45 of the disclosure! Manning itself recognizes this breadth at page 45:

> It is readily apparent that formula 1 encompasses a wide variety of heterocyclic nitrogen-containing compounds. Illustrative heterocyclic nitrogen-containing compounds within the scope of formula 1 which may be used for reducing transpirational moisture loss from plants and increasing crop yield are included in Tables 1 through 43 below.

Tables 1 through 43 extend from page 46 through 238. Thus, for the sake of perspective, the compound on page 117 relied on by the examiner as as starting point for further modification is only 1 of 5 compounds depicted on page 117, which is one of three pages of Table 14, and Table 14 is one of 45 Tables which extend from page 46 to page 238 of the specification.

Thus, in order to make a compound within the present claims from the Manning disclosure, the skilled person must first serendipitously select the bottom compound on page 117 out of all the compounds disclosed on pages 46 to 238, for which no particular guidance or suggestion is given. The skilled person must then somehow be motivated to modify this compound in a very specific manner out of the myriad of possible combinations and permutations of rings and substitutents for generic formula 1 in the massive lists covering pages 5-45, to select not only replace the particular substituents of the compound on page 117 that differ from the presently claimed compounds, but also change the position of the 8-position substituent of the page 117 compound to the 7-position. Moreover, it is apparent from the enlargement of group R'_{12} at the 8-position of the page 117 compound that this is a massive group:

$$—O—(CH_2CH_2O)_7—$$

having seven repeats would be a substantial change from the present compounds which require a hydrogen at the 8- position by the -H specifically shown at this position in formula II of claim 18. The Examiner proposes that the skilled person would be motivated to move this 8-position substituent to the 7-position, on the basis that the generic teachings with respect to Z show that they can be at any position. However, the Examiner apparently did not recognize that this Massive 8-position substituent in the page 117 compound is also far

apparently did not recognize that this massive 8-position substituent in the page 117 compound is also far outside of the scope of R^2, the 7-position substituents permitted in the presently claimed compounds.

Again, it is respectfully submitted that there is no guidance or suggestion anywhere in this reference that would motivate the skilled person to modify the page 117 compound (in the unlikely event that it was selected for modification in the first place) to make the combination of substituent replacements and ring-position changes that would be necessary to achieve any compound within the scope of Applicants present claims.

Accordingly, it is respectfully submitted that the Manning reference does not in any way give rise to *prima facie* obviousness. Its generic breadth is *so broad* and *so all-encompassing* that, considering its lack of guidance, it effectively teaches no more than the compounds that are specifically named or illustrated. Moreover, considering the massive number and diversity of named compounds, there is no guidance or other reason why the skilled person would particularly select the claim 117 compound, and even if for some unknown reason this compound was chosen for further modification, there is no guidance or other reason that would motivate the skilled person to make the combination of multiple substituent and positional modifications that would be required to arrive at a compound within the present claims.

The Federal Circuit has made very clear that the burden is on the Patent and Trademark Office to establish a prima facie case of obviousness in the first instance. It is a fundamental principle of the patent laws that a prima facie case of obviousness has not been made unless it is demonstrated that persons of ordinary skill in this art would have been motivated by the prior art to select the particular claimed species or subgenus from the disclosed prior art genus. In re Ochiai, 71F.3d 1565, 1569-70, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); Deuel , 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art."(emphasis in original)); Jones, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897,1901 (Fed. Cir. 1990)(in banc); In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258

(Fed. Cir.1984)("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").

Accordingly, it is respectfully submitted that the Examiner has not met the PTO burden of establishing prima facie obviousness with respect to any of the cited references, and the rejections under 35 U.S.C. § 103 should be withdrawn.

Claim Rejections under Section 112

It is respectfully submitted that all grounds for rejection made at page 6 of the Action have been obviated or overcome by the above amendments to the claims. The objected-to parentheses have been removed from claim 18, and the inadvertently retained "halogen" has been removed from the definition of R^2 in claim 9. Accordingly, withdrawal of these grounds for rejection is believed to be in order and is respectfully requested.

Conclusion

It is believed that all ground for rejection have been addressed and overcome by the above Amendments and the foregoing remarks. Accordingly, withdrawal of all grounds for rejection and the allowance of all claims are respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: August 10, 2005 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk